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13. ABSTRACT *(Maximum 200 Words)*

Women with breast cancer who receive psychosocial interventions may have longer disease-free and total survival. Psychological distress seems to be particularly acute in younger women with breast cancer, a population that seems particularly amenable to psychosocial interventions. In designing studies to test for the effects of interventions aiming to alter psychological state, there are concerns that inferences may be hampered by the need to control for non-specific (therapy-related) factors. For this reason, the BRIDGES study was designed with two control groups; a conventional, no-treatment control and an intensive dietary intervention attentionally equivalent to the active mindfulness meditation-based intervention (SRC). Data collection for this three-armed study was completed in April 1999. Results indicate an overall beneficial effect of the SRC that was persistent over time and stronger in women with high baseline emotional distress. Nutrition-related effects were associated exclusively with nutrition-related outcomes, indicating that the SRC effects were specific to that intervention and not just due to non-specific therapy-related factors. There were no effects observed in the usual care control group. Numerous presentations have been made on the findings from this study and the major outcome papers are in various stages of completion, as of this Final Report.

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PI - Signature Date

TABLE OF CONTENTS

INTRODUCTION

An increasing body of research literature has shown that psychological states have an impact on recovery and quality of life in women with breast cancer. Psychosocial variables such as emotional expression, coping styles, and factors related to social support appear to have the most promise for improving quality of life and increasing the probability of prolonged survival. There also is a small body of evidence indicating that women with breast cancer receiving psychosocial interventions may have longer disease-free and total survival. Psychological distress seems to be particularly acute in younger women with breast cancer, a population that seems particularly amenable to psychosocial interventions. This is due, in part, to the fact that younger women with breast cancer tend to receive more aggressive treatment and to have a worse prognosis than older women who have less virulent forms of the disease. It is often their first experience with serious illness and younger women tend to have more concern with issues related to body image and major disruptions to typically very busy lives.

In light of these findings, there is an important need for the development of cost-effective psychosocial interventions for women with breast cancer. At the time we wrote the proposal, we determined that a successful intervention would be one that could reduce emotional distress, promote effective coping with diagnosis and treatment for breast cancer, and be useful and adaptable to the diverse population of younger women with breast cancer. The recently completed study successfully sought to adapt the University of Massachusetts Medical School's Stress Reduction Clinic Program (SRC) for younger women with breast cancer. The SRC is a well-established intervention program with demonstrated effectiveness in improving emotional status and quality of life in individuals with a variety of serious medical problems. The program is educationally based and has been conducted in a variety of health care settings with diverse populations.

Our research addressed aspects of two of the fundamental research issues in psychosocial effects of breast cancer and the role of our well-recognized (but hitherto untested in this population of patients) SRC intervention in quality of life and status of immune parameters that may themselves be important in determining disease prognosis. Specifically, this research was designed to: 1) examine the psychosocial impact of breast cancer; and 2) identify techniques for delivering cost-effective care to facilitate recovery, improve immunologic response, and improve quality of life after treatment for breast cancer.

Overall Goal

The primary goal of this proposal was to test the efficacy of the well-established, short-duration mindfulness meditation-based SRC in women under 65 years old diagnosed with newly diagnosed Stage I and Stage II breast cancer. The SRC intervention aims to influence a number of well-defined psychosocial factors which are suggested by a growing body of evidence as critically important for: adjustment to a potentially life-

threatening diagnosis; enhancement of quality of life; and potentially, for enhancement of resistance to disease progression and survival in women with breast cancer. The study consisted of a prospective randomized three-arm design with the aim of enrolling 60 women into each arm: 1) the SRC intervention, tailored to focus on issues specific to this population; 2) a nutrition education program (NEP) which would serve as an inactive attention control with regard to the psychosocial outcome measures and as a potentially active intervention with regard to effect on immune parameters (see Specific Aim 2); and 3) a usual care control group.

Specific Aim 1: To test the effect of SRC on Quality of Life (QOL), emotional awareness and expression, coping strategies and related perceptual and behavioral factors, and compliance with the intervention and with medical recommendations in women (under 65 years old) with newly diagnosed Stage I and II breast cancer. Because the SRC and NEP groups would have an equally intense group session component and the NEP group will receive none of the essential components of the SRC, the test between the two groups, SRC and NEP, would distinguish between the effect of the SRC intervention and non-specific group/therapist factors.

Primary Hypothesis: The SRP intervention will result in improved QOL and ability to cope, compared either to the NEP or to usual care alone.

Secondary Hypothesis: The SRC intervention will result in: a) improved perception of self and self in relationship to the world, as measured by increased self-esteem, sense of coherence, and decreased loneliness; b) a corresponding reduction in mood disturbance (e.g., anxiety and depression); c) increased use of active-behavioral and active-cognitive coping strategies, as measured by the Dealing with Illness Coping Inventory; and d) increased compliance with treatment regimens as compared to usual care alone.

Specific Aim 2: To test the relative effect of the SRC versus NEP and usual care on immune parameters specifically related to cytokines that activate Natural Killer (NK) cells and melatonin levels that may in turn affect response to breast cancer (1). Because NK activity may be related to recurrence (2) we have previously shown that low-fat diets enhance NK activity (3) and we have preliminary data indicating that meditation may affect melatonin levels in women, we are particularly interested in relative differences between the two test groups, SRC and NEP, compared to usual care alone.

Specific Hypothesis: Relative to usual care, the SRC intervention will increase the immune responsiveness of Stage I and II breast cancer patients. This will result in an increase in the production of cytokines, e.g., Interleukins 2 and 4 (IL-2,4), which activate NK cells, and interferon (IFN)γ, which activates macrophages.

Specific Aim 3: To determine if the study effects (described in Aims 1 and 2), along with maintenance of the intervention practices, persist over 1-2 years of follow-up.

Specific Hypothesis: Psychosocial and immunologic changes will be maintained over time and related to on-going practice of the SRC and NEP dietary practices, self-regulatory strategies and behaviors.

WORK ACCOMPLISHED

It is important to note that when the grant was written, we stated that women who were under fifty years of age would be entered into our study. We extended this criterion to include any women who is under sixty-five years old at time of diagnosis with breast cancer. The reasons for extending the age requirement are as follows: 1) typically women work until they are sixty-five years old, which means they lead lives as busy as those of women under age fifty; in fact, we find they often are busier in respect to career development; 2) we found that these women also have concerns with issues related to body image; and 3) we had no reason to believe that these women would not obtain the same benefits from the interventions. The age of 65 years provides a natural and culturally widely appreciated demarcation between early middle age, and its concomitant demands and pressures, and late middle age, with its progressive decline in terms of life pressures.

Because the Statement of Work contained in effect at the time the grant was awarded, provides the framework for all activities undertaken since that time, we employ it here as the outline of all progress.

Task 1: Run-in Phase. Months 1-3

a. Additional focus groups and preliminary data will be gathered as needed.

   Weekly meetings were held for the first 6 months of the study. These were always attended by the four site coordinators and two Co-Principal Investigators from the University of Massachusetts. In the first 3 months, other investigators (mainly oncologists and surgeons) also attended the meetings. At these sessions, recruiting protocols were developed and patient communication and other issues were discussed and resolved. It was determined that sufficient preliminary data were collected prior to the grant application process in order to guide planning of the recruitment protocols and data collection instruments. Therefore, additional focus groups were not held.

b. Based on focus group and preliminary studies, introductory and booster (therapy) sessions will be developed so that the content of the program will be most useful to younger women with early stage breast cancer.

   Introductory and booster sessions were developed. We determined that there would be two introductory sessions for the SRC intervention. At these sessions, women discussed their experience with breast cancer and started learning about mindfulness-meditation. There were an average of twelve women in each of these groups. The

size of the groups allowed them to support one another's experiences and enabled them to bond so that when they attended the SRC classes they were likely to know someone in their class. These sessions gave the women a chance to meet and talk with others who were experiencing the same illness. It also allowed them to ask questions or talk about whatever was important to them. There were four booster sessions which were held after the standard SRC classes. At these sessions, women learned more about meditation and yoga, discussed their experiences in the SRC and continued to discuss their experiences with breast cancer. These sessions served to review and reinforce what they had learned in the SRC and gave the women a chance to talk about issues of personal concern to them.

c. The Nutrition Education Program will be developed using the recently funded Women's Health Initiative as an appropriate low-fat model.

The Nutrition Education Program (NEP) was to be developed using the recently funded Women's Health Initiative (WHI,) as an appropriate low-fat model. It was decided that we could design and implement a low-fat intervention superior to that of the WHI. Therefore, we invested the necessary resources and developed a program specific to BRIDGES. The NEP consisted of an overview of diet and health with an emphasis on how change in diet can affect well-being and how it broadens, rather than narrows, dietary options. The program was held at a location close to the University of Massachusetts Medical School in Worcester and consisted of 14 weekly sessions, each ninety minutes long. There was an additional session on a Saturday or Sunday which lasted six hours. The participants were asked to do various homework (cooking and nutrition) assignments which helped them to incorporate the program information into their daily life. At these classes the women did hands-on preparation and tasting of low-fat, high-fiber foods. They were taught alternative methods of creating and enhancing flavors, including the use of spices and herbs. The transition to low-fat eating also entailed increased consumption of vitamins and minerals. The role of these nutrients plus various spices in health were discussed. The individuals assigned to this intervention developed personal eating plans and dietary goals so that they reduced the amount of fat in their diet to less than twenty percent of the calories that they eat.

d. Instrument material will be piloted and finalized, where appropriate. Reliability tests will be conducted when necessary.

Because all instruments had been validated and checked for reliability in previous studies it was not necessary to conduct separate reliability tests for BRIDGES. All instrument materials were piloted and finalized as stipulated in the protocol. Most of the instruments are being used in our other studies and all have performed well in previous tests of validity and reliability. We omitted the interviewer-administered questionnaires (i.e., the Hamilton Anxiety and Depression Scales) because they were redundant to other self-assessment data. Copies of these instruments were included in the appendix of the original submission and modified forms currently in use in the

study were included in the appendix of last year's annual report. Below is a list of instruments being utilized.

Baseline questionnaire Measures include: Background and Demographic Data: age; sex; marital status; education; number of children; number and dates of pregnancies; breast feeding history: (months for each child); and menopausal status (including surgical menopause). Personal Health History: present medical/psychiatric history and treatment (including history of exposure to estrogens, oral contraceptives, unusual menstrual problems). Family Health History: history of breast cancer; history of other cancers. General Self Care: sleep; exercise frequency; and smoking status.

Besides data collected on the baseline instrument we also administered these other questionnaires:

Beck Anxiety Inventory
Beck Depression Inventory
Sense of Coherence
Revised UCLA Loneliness Scale
Rosenberg Self-Esteem Scale
Functional Assessment of Cancer Therapy (FACT)
Mini-Mac Scale
Dealing with Illness
Marlowe-Crowe Social Desirability (MCSD) scale (Personal Reaction Inventory)
Symptom Check List
Social Readjustment Rating Scale
Social Approval
Seven Day Dietary Recall (7DDR)

e. An introductory videotape (to be used for recruitment) will be produced.

Dr. Ockene directed this task. During the weekly meetings (which were discussed in 1a) the purpose of the video, along with the content of the script, was discussed. The Project Coordinator and a representative from each site were videotaped. The video is five minutes long. It includes information about the funding source, why the study is important, and how the study is designed. It was shown to most of the women who were interested in joining the study. The videotape and script were included in the appendix of the1997 annual report.

f. The Project Coordinator will be hired and trained in conducting phone and in-person interviews by Drs. Clemow and Massion.

The Project Coordinator, Susan Druker, was hired. Due to her skills in conducting interviews, the training session was not needed. Also, as noted above, we decided not to include in the battery of psychosocial instruments the Hamilton Anxiety Scale and

the Hamilton Depression Scale. Both of those scales are administered verbally. Ms. Druker worked with the three other site coordinators in developing numerous study protocols including ones for periodic interviewing.

g. A database to be used in the will be constructed.

This task was completed. The biostatistician, Thomas Hurley, along with a research fellow Jay Fowke (who was hired part-time to assist with data management) developed a plan for our database. Dr. Fowke has completed his Ph.D. in Epidemiology from the University of Massachusetts and joined the faculty of the School of Public Health, University of South Carolina (USC) and the South Carolina Cancer Center as a Research Assistant Professor on 10 January 2000. He will continue studying breast cancer under James R. Hebert, Sc.D., Professor and Chair of the Department of Epidemiology and Biostatistics at USC.

All data collection steps have been completed. All data are within range, and have good internal logic. A formal data management plan for BRIDGES was completed and implemented. After identifying all the sources of data we were collecting, Dr Fowke created the data entry programs for all data not collected via optically scanned instruments. Along with Thomas Hurley, he determined the location for storage of data entry-files, the choice of data entry personnel, the timetable for data entry, quality assurance steps, and the timing for the backup and archiving of the analytic datasets.

h. Analysis of available run-in phase data will be done by Drs. Hebert and Massion. We conducted process-related analyses (to assure data collection steps occurred) and performed simple univariate analyses.

Task 2: Recruitment. Months 4-21:

a. 180 women (age <50 years) with Stage 1 or 2 breast cancer from Worcester, MA and Providence RI will be recruited as participants for the study.

178 (99% of the recruitment goal) individuals were enrolled into the study. As discussed previously, we extended the age eligibility to women who were diagnosed with Stage 1 or 2 breast cancer at age 65 or less. A patient brochure was developed along with a letter that is signed by one of their physicians in order to assist with recruitment.

17 (8.5%) have dropped out of our study. We estimated that our retention rate would be 80%. Our high retention rate was due to the positive response of our patients to this study.

b. Baseline measures will be taken on all study parameters as stated in the protocol.

A baseline questionnaire was developed as described in previous reports. The following anthropometric measures were taken at baseline: height; weight; sitting height; and waist and hip circumference. Blood samples also were drawn and twenty-four hour urines were collected. The medical questionnaire was to be used to collect information on: date of first positive cytology or positive biopsy; if individual had radiation, when and if there were major complications; what type of surgery was performed (i.e. lumpectomy alone, mastectomy, etc.); histology; tumor size; tumor grade; tumor differentiation; axillary nodes samples; estrogen/progesterone receptor concentrations; stage of breast cancer and information about their chemotherapy treatment. A nutritional assessment was completed by all participants. For this, we used a seven-day diet recall (7DDR) (4).

c. Study subjects will be randomized into one of the three arms of the study 1) Stress Reduction and Relaxation (SRC); 2) Nutrition Education Program (NEP), and 3) Usual supportive care(UC).

Study subjects were randomized into one of the three arms of the study 1) the Stress Reduction (SRC); 2) the Nutrition Education Program (NEP), and 3) Usual supportive care (UC). We call the UC arm, the Individual Approach Condition and state in our patient brochures that they choose whatever strategy to cope that they think is best for them. An eligibility requirement form that was developed continues to be used. Of the 178 subjects randomized 60 were enrolled into SRC, 59 into NEP and 59 into UC.

Task 3: Intervention. months 6-27;

a. Participants will become involved in the intervention arm to which they are randomized. The SRC and NEP will be given four times per year at UMMC.

The interventions were given three-times per year. Six interventions were offered, all lasting 14 weeks. We decided to add another intervention in order to achieve our goal of recruiting 180 women. This decision was reached due to two of the participating institutions falling short of their recruiting goals. Each institution was to recruit 45 women. Because of its distance to the University of Massachusetts Medical School, one institution recruited only 16 patients. The other institution, which fell short of its goal, recruited 30 patients. The women involved in SRC and NEP gave rave reviews of the interventions. Throughout the term of the study, we contacted them on a monthly basis to obtain feedback and, without exception, everyone stated very positive things about being involved in the study.

b. Just prior to the interventions (or time-controlled for the women randomized to usual care) all parameters (except immuno-endocrine measures and diet) assessed at baseline will be reassessed just prior to the intervention and at four, 12, and 24 months from this pre-intervention measurement point.

Because of budgetary restrictions prior to final approval, we reduced measurements from five to four times over the period of each woman's involvement. To make best use of resources, we decided that all baseline measures (see 2b) would be taken just prior to the interventions. Therefore, there was no need to reassess these measures prior to the interventions. We collected 177 complete baseline measures, 158 four-month measures, and 138 one-year measures, the definitive endpoint. Other data subsets have even greater levels of completion. Therefore, for analyses that do not require complete data on each subject, larger numbers would be available.

c. The SRC group will receive the standard SRC segment plus additional therapy sessions for a total of fifteen sessions. The SRC group received the standard SRC segment plus additional therapy sessions for a total of fifteen sessions. As stated previously, two introductory sessions plus four booster sessions were required for all women who enter the SRC arm of the study. For more information see 1b.

d. The NEP group will receive their intervention on approximately the same schedule as women in the SRC arm of the study.

The NEP group received their intervention at the same time as the women in SRC. Nutrition classes and SRC classes lasted for fourteen weeks and began and ended at the same time.

Task 4: Follow-up months 8-46;

a. All participants will be assessed just after the intervention (or time adjusted for all women in the UC) and at twelve months and twenty-four months after recruitment. Assessment will include all the psychological and quality of life measurements, as well as immuno-endocrine parameters and the nutritional assessments. At twelve months melatonin will be assessed. Nutrition assessments will be made only at the twelve month and twenty four-month post recruitment points in order to account for seasonal differences in dietary intake.

All participants were assessed just after the intervention (or time adjusted for all women in the UC) and at twelve months and twenty-four months after baseline. Assessment includes all the psychological and quality of life measurements, as well as immuno-endocrine parameters and the nutritional assessments. At four and twenty-four months, melatonin was assessed. Nutrition assessments also were made at four months, twelve months, and twenty-four months after baseline. We decided to conduct the nutritional assessment at four months because the information gathered provided us with data as to whether women have changed their diet immediately subsequent to the intervention. Monthly phone calls also were utilized to gather data. It was during these phone calls that we checked for compliance with the SRC protocol.

b. On-going data collection, review for completeness, and preliminary testing of study hypotheses will occur.

All site coordinators reviewed the questionnaires for completeness. The process of entering the data was completed in 1999. Much of the data were optically scanned. All data were successfully entered, cleaned, and made part of archival datasets.

Task 5: Final Data Analysis, Months 47-51

a. Perform all exploratory analyses to test for adherence to model assumptions.
b. Perform all data simplification tasks (e.g. principal components analysis).
c. Test study hypotheses.
d. Conduct post-hoc analysis of study data.
e. Prepare manuscripts.

All data were tested for adherence to models assumptions. Where violations were evident (e.g., heavy right-skewing in the cytokine data), the appropriate statistical adjustments (e.g., log-transformation) were made. It was deemed unnecessary to simplify data beyond the construction of summary scores (i.e., the standard procedures) for the psychosocial measures (e.g., the SCL-90 scores). We are currently finalizing the major results papers from this study and have begun post-hoc analysis of study data, an activity that typically continues for many years after the active data collection phases of large-scale epidemiologic studies.

Synopsis/Listing of Results

In our first annual report we stated that various preliminary data [1, 5] and theoretical considerations [6, 7] had been published.

Two book chapters have been written where BRIDGES is discussed. The first book chapter is in the Textbook of Psycho-Oncology [8]. This describes the SRC intervention and its application in oncology. BRIDGES is mentioned as an on-going study. The second book chapter was published in Melatonin in Psychiatric and Neoplastic Disorders [9]. This chapter discusses our hypotheses about melatonin and meditation. BRIDGES is discussed and preliminary data are provided.

In April 1997, we presented an abstract at the Society for Behavioral Medicine meeting. This was a preliminary report (n = 75) of baseline and four-month scores on psychosocial measures. This abstract was included as an appendix to the 1997 Annual Report.

Dr. James Hebert was invited by the editor of Advances to provide comments to an article written by Keith Block. Dr. Block runs an alternative cancer treatment center in Illinois. Dr. Hebert provides an epidemiologist's view of Block's challenge by discussing his role

as a reviewer of Department of Defense breast cancer grant applications and the grant application review process. BRIDGES is mentioned (6).

Dr. Lynn Clemow presented at a breast cancer conference in September 1997 sponsored by the Cancer Center of the University of Massachusetts Medical School. This was a preliminary report (n=157) of baseline, four-month, and one-year scores on psychosocial measures and dietary behavior. The abstract was attached as an appendix to the 1998 Annual Report.

Dr. Ann Massion presented at a Symposium sponsored by the American Psychiatric Association on May 19, 1997. At this annual meeting she presented baseline and fourth month data on psychosocial measures.

Dr. James R. Hebert also provided comments to an article written by Dr. Theodore Pincus "Analyzing Long-term Outcomes of Clinical Care Without Randomized Clinical Trials: The Consecutive Patient Questionnaire Databases" (7, 10).

Drs. Lynn Clemow and Ann Massion presented a poster at the Era of Hope Conference in 1997. Results presented were based on data from 157 women who had completed the 4-month assessment point. Both psychosocial and dietary behavior results were discussed. The abstract was attached as an appendix to the 1998 Annual Report.

For the 1999 Society of Behavioral Medicine Meeting held in San Diego, CA, in March of 1999, we submitted two abstracts. "Change in Diet and Body Mass Following Intensive Intervention in Early-Stage Breast Cancer" (11), outlining the major nutritional findings of this study, was presented by Dr. James R. Hebert. The other, "Which women with breast cancer benefit most from a meditation-based stress reduction intervention: baseline distress and expectancy" was presented by Dr. Lynn Clemow.

The major dietary and nutritional findings for this study have been provisionally accepted for publication by the Journal of the American Dietetic Association. A copy of this article is included as an appendix to this Final Report.

The two other major papers from this study and their current status are as follows:

1. "A Meditation-Based Stress Reduction Intervention for Women with Breast Cancer: Psychosocial Outcomes and 1- Year Follow-Up," is in penultimate draft form. It is included here as a draft manuscript. We are finalizing this and should have it under review by mid-March 2000.

2. The paper describing the cytokine outcomes is currently in progress. It is provisionally entitled "The Effect of Intensive Meditation and Dietary Interventions on Cytokines Involved in the Immune Response in Women with Early-Stage Breast Cancer." Analyses thus far indicate a marginally significant improvement in Interleukin 2r levels in women

randomized to the SRC (relative to either of the other groups). Further analyses are being undertaken to examine interactions with patient-specific factors including motivation, expectation, and intervention compliance.

The results based on the melatonin analyses are subsumed under the Career Development Award of Dr. Ann Massion and are described in her Final Report. It is anticipated that the final report of those analyses will be completed in 2000.

Numerous other analyses are on-going. Some of these are directed at the two-year data. While these were not, and continue not to be, the definitive endpoints, they will be instructive regarding the persistence of effects that were observed at the one-year point.

Summary of Results

Psychosocial Well-Being (also see the paper included in the appendix): To date, the SRC intervention appears to produce the most consistent improvements in psychosocial well-being. The no-treatment control group (UC) appears to be associated with a slight deterioration and the NEP is associated with psychosocial outcomes intermediate between the SRC and UC groups. For example, we observed an increase of 1.4 vs. very little change (+0.7) in NEP and a reduction of -1.9 in UC (p=0.0007) in active-cognitive coping on the Dealing With Illness scale. Other variables which showed similar significant results for SRC are Depression (Beck and SCL-90-R), Spirituality (FACT-B), Helpless/hopeless thoughts (MAC), Emotional Expression (Courtauld scale), and emotional distress (SCL-90-R GSI and five subscales). Social support and Active-cognitive coping were significantly better in the NEP than UC group. The usual effect size (pre-post GSI on the SCL-90-R) for the standard UMass Stress Reduction Program in published studies in a variety of populations of self-selected participants (immediate treatment vs. wait-list controls) [12-15] ranges from -0.25 to -0.57 (34-54% change). In this study, using an augmented version of the same program, the intervention produced a reduction of 0.12 (roughly 25% change) suggesting that the treatment effect might be larger in a design with Breast Cancer patients who select SRC instead of being randomly assigned to it.

At one-year follow-up, we found significant sustained benefits of the SRC condition on Spirituality, Active-Behavioral Coping and Emotional QoL on the overall sample [16]. In an effort to explore the individual differences that may have modified the intervention effects (particularly those that might bear on the process of self-selection) we have conducted some preliminary subset analyses. Women with high baseline emotional distress (Beck Depression scores> median) were much more likely to benefit significantly at post-treatment and to have a more enduring effect after one year of the SRC vs. comparison conditions on a variety of psychosocial measures including : Higher Active-behavioral (p=.01) and Active Cognitive Coping (p=.03) and lower Avoidant Coping (p=.008); Less Helpless-Hopelessness (p=.04); higher Spirituality (p=.01) and Emotional

QoL (p=.005), higher social support (p=.003), and less distress on the GSI and 6 subscales of the SCL-90-R.(p=.05-.01).

Diet-Related Outcomes (also see the paper included in the appendix): Of all women randomized, 154 had complete baseline, 4-month (immediately post-intervention), and 12-month dietary data and 159 had body weight data for each time point. Though not focused on weight loss, we sought to examine change in weight partly because of the importance of weight as a prognostic indicator and partly as a construct validation of the dietary data. Changes in percent of energy as fat (%EF) and body weight (kg) were analyzed using PROC GLM in SAS, controlling for baseline value of the dependent variable. At 4 months, there were decreases of 5.6%EF and 1.3 kg in weight in the NEP versus slight increases in the SRC and UC (p=0.0002). At 12 months there was a slight rebound in fat intake in the NEP (4.5%EF less than baseline versus no change in the SRC or UC, p=0.008) but women had returned to their baseline weight. In 50% of women with high expectation there was a larger reduction in fat (-6.0%EF and –5.0%EF at 4 and 12 months, respectively, p<0.01), but the same pattern in terms of body weight change. The results of this study show that large reductions in dietary fat can be achieved in such an RCT and that the effect is larger in women who expect more of an effect from the intervention, indicating effect modification of the intervention by expectancy. Weight shows a pattern typical of many diet interventions, but it is notable that the weight gain typical of early-stage breast cancer patients was not observed [17]. Both of these findings could translate to improved survival over time [18].

Melatonin Excretion: Overall, results have been consistent with increases in both the SRC (+1.21 *u*g/day) and NEP (+1.54) and a decrease in the UC (-0.38), but not close to "statistically significant" (p=0.49). In terms of magnitude of change, they are about one quarter to one half the size observed in our previous studies. Analyses are currently underway on the 2-year data. It is anticipated that Dr. Massion will finish this manuscript during the Spring of 2000.

CONCLUSIONS

In summary, progress of this grant has been excellent. Recruitment ended in December 1996 with a total of 178 subjects (99% of the recruitment goal). Governance for the study functioned smoothly, with most executive decision making occurring in a small working group consisting of Drs. Hebert and Massion and Ms. Susan Druker. Day-to-day operational issues were decided mainly in the site coordinator's working group, which was chaired by the Project Coordinator/UMASS Site Coordinator, Ms. Susan Druker. Because Susan Druker was a member of both of the functioning working groups, communications within UMMC site and across the four sites were extraordinarily smooth and efficient. The overall Steering Committee Meeting met two times in each of the years of the study. Occasionally, an executive decision came out of these meetings. However, it transpired that its main purpose was to provide information to investigators at the other sites and to maintain enthusiasm in the study. Although there was no place to mention this above, it should be noted that the level of enthusiasm for this study and the dedication about which people feel regarding their own involvement and involvement in their patients has never been higher in any study with which I (James R. Hebert) have been involved.

One of our major concerns in designing this study concerned issues around the asymmetry of intervention conditions where blinding is not possible. In the years of meetings before we formally proposed this study, we spent more time on this issue than anything else. Our concern was that an obvious imbalance between the intervention conditions would either lead to a low recruitment rate or there would be large differential dropout after women were randomized. With recruitment completed and having developed the interventions, we can confidently say that this was not a problem.

I appreciate the opportunity to convey the excellent progress that we made in this study. Please let us know how we can keep the program office apprised of progress regarding on-going papers.

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CHANGE in DIET and BODY MASS FOLLOWING INTENSIVE INTERVENTION in EARLY-STAGE BREAST CANCER

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CHANGE in DIET and BODY MASS FOLLOWING INTENSIVE INTERVENTION in EARLY-STAGE BREAST CANCER

ABSTRACT

Objective To determine the effectiveness of an intensive dietary intervention on body mass and diet in women with breast cancer.
Design Randomized clinical trial.
Subjects 178 women aged 20 to 65 years diagnosed with stage I or II breast cancer.
Intervention An intensive dietitian-led 15-group session Nutrition Education Program (NEP), focusing on low-fat, high-fiber, nutrient-dense dietary practices, was compared to: the UMass Stress Reduction Clinic's program of mindfulness-based stress reduction (SRC); or usual supportive care (UC).
Main outcome measures Dietary fat, complex carbohydrates, fiber, and body mass.
Statistical analysis Simple univariate statistics were computed to describe the study population. Analysis of variance (ANOVA) was conducted to test for differences according to intervention group.
Results Women randomized to the NEP (vs. either SRC or UC) experienced a large reduction in fat consumption (6.1% of energy as fat (EF)) at 4-months (immediately post intervention) and much of this reduction was preserved at 1 year (4.2%EF) (both $p<0.0001$). There was a 1.3 kg reduction in body mass at 4 months in the NEP vs. no change in the SRC and UC ($p=0.005$). In the subset of women who had higher-than-average expectation of a beneficial effect of the intervention, changes were larger.
Applications Results indicate the effectiveness of a dietitian-led intervention in helping breast cancer patients improve diet is more pronounced in women with high expectations, indicating that personal factors may have an important role in modifying the effect of such a behavioral intervention and arguing for future research into the role of expectation in diet interventions.

CHANGE in DIET and BODY MASS FOLLOWING INTENSIVE INTERVENTION in EARLY-STAGE BREAST CANCER

INTRODUCTION

Epidemiologic evidence indicates that environmental, not genetic, causes dominate as plausible explanations for inter-population differences in breast cancer rates, change in rates over time, and differences in prognosis (1-5). In terms of breast cancer prognosis, the strongest and most consistent of these extrinsic factors are diet-related. The factors associated with increased risk are those indicative of metabolic overload including energy density of the diet, animal product consumption, and obesity (5-7). Those associated with decreased risk include foods of vegetable origin (6, 8-13) such as soy products which contain phytoestrogens that can affect circulating estrogen concentrations and modulate cellular processes by competitively binding at estrogen receptor sites (14-18); foods high in fiber (19-21); and foods rich in dietary carotenoids and other similar compounds that may affect tumor expression of estrogen receptors (ERs) (22) and immune response (23).

An important preliminary step toward studying the effects of dietary change on breast cancer outcomes is the development and testing of a dietary intervention that can assist women in making changes of a magnitude sufficient to alter disease progression. Adherence to dietary behavior change programs typically has been difficult to achieve (24, 25). The rare successes have been highly intensive and of long duration, involving extensive support systems (26-29).

Besides the direct effects of a healthful diet on secondary prevention, there are a number of psychological benefits such as improved self-esteem, self-efficacy, and mood that may derive from an individual's ability to change her behavior and to maintain that change (30-33). This appears to relate specifically to a more healthful dietary change (34, 35). Because sensations of taste and smell are primary in the experience of food (36, 37) and those sensations are processed in a part of the brain associated with emotions (38), the role of psychological factors could have import for food-related behaviors. Mood improvements also could result from increased or decreased consumption of certain food components including fat, fiber, and carbohydrates. Psychological factors also may influence adherence to dietary change (35, 39-41).

Despite the popularization of diet – cancer hypotheses in the lay press (42) and in broadcast media, little spontaneous dietary change apparently takes place among women with breast cancer. In fact, it has been noted that women with breast cancer generally gain weight at a higher rate than women in the general population (43), a trend that may be related to poorer disease outcome (5, 44-47), possibly via an effect of overweight on steroid hormone metabolism (48-51). The purpose of this paper is to report on the effect of an intensive dietary intervention delivered as part of a randomized clinical trial (RCT) on dietary factors (including fat, complex carbohydrates, and fiber), and body mass.

METHODS

The Breast Research Initiative for DeterminiG Effective Strategies (BRIDGES) for Coping with Breast Cancer was an RCT into which 178 women diagnosed with breast cancer were enrolled from four practice sites (The University and Memorial Hospital Campuses of the UMass Memorial Medical Care System, Worcester, MA; Fallon Community Health Plan, Worcester, MA; and Miriam Hospital, Providence, RI).

Eligibility: Women eligible to be in this study were: 1) newly diagnosed (within two years) with stage I or II cancer of the breast; 2) between 20 and 65 years of age; 3) capable of understanding informed consent in English; 4) planning to remain in the study area for at least two years following recruitment; 5) Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2 (i.e., able to function normally >50% of the time); 6) willing to accept randomization; and 7) had a working telephone and were willing to be contacted at home for assessments regarding program adherence and psychological factors. Specific exclusion criteria included: 1) a previous diagnosis of cancer in the past five years, except non-melanoma skin cancer; 2) current chronic substance abuse (either drug or alcohol, e.g., >3 drinks/d more than 3d/wk); and 3) past or present psychiatric or neurologic disorder that would preclude or severely limit participation in the study (e.g., major depression, schizophrenia, organic brain syndrome, psychosis, or significant cognitive impairment).

Randomization: Once enrolled, women were randomized into one of three study conditions: a mindfulness-based stress reduction program that used the Stress Reduction Clinic Program (SRC) of the UMass Medical School Center for Mindfulness as its centerpiece; an intensive dietary intervention known as the Nutrition Education Program (NEP); or usual supportive care (UC). Each of the interventions was delivered at a single site in Worcester, MA.

Description of the Randomization Conditions: The registered dietitian (RD)-implemented NEP uses intervention strategies that are based on the principles of social cognitive theory (30-33) and patient-centered counseling (52). The primary objectives of the NEP are to: 1) increase patient awareness of dietary risk factors associated with breast cancer; 2) increase patient knowledge of nutrition in the context of a diet that is ~20% of energy as fat and high in fiber and micronutrients obtained from a variety of plant sources; 3) increase patient confidence (i.e., self-efficacy) in her ability to make dietary changes; 4) enhance patient behavioral and cognitive skills for adherence to a low-fat, high-fiber plan for eating; and 5) provide group support in making dietary changes. It consists of: two individual sessions, one of 60 minutes at the beginning of the program and one of 30 minutes at the end; and 15 group sessions, of which 14 are 150 minutes in length and 1 is a 5.5-hour, all-day session. Its high intensity aims both to achieve and maintain a lower consumption of fat and to provide a level of participant contact approximately equivalent to that of the SRC. The 15 group classes are held over a 15-week period. From a nutritional perspective, classes focus on fat and fiber (because of their importance in both immune function and endocrine metabolism as well as in the public perception of their importance) in addition to increasing the nutrient and 'functional constituent' densities of the diet by substituting fruits, vegetables, whole grains, and low-fat meats and dairy products for high-fat foods and by encouraging little or no alcohol consumption. Topics covered include: vegetarian meals, vitamins, minerals, specific functional components of foods that can regulate metabolic processes associated with carcinogenesis (e.g., indoles, lignans, antioxidants, phytoestrogens), caffeine, alcohol, herbs, and spices. Recognizing that each woman will learn material in her own way, the program attends to the driving forces of taste, smell, appearance,

and texture of foods in addition to including didactic material. Women are taught to glean required information from food labels, and they are taken to local grocery stores for a "hands on" lesson in comparison shopping. Healthy cooking methods included stir frying, pressure cooking, microwaving, and steaming, as well as judicious use of herbs and spices that carry flavor in place of fat. Since food intake permeates all facets of life, dietary lifestyle interests and concerns are addressed.

Although there is evidence that body mass may affect disease prognosis (5), reduction in body mass is not a primary goal of the NEP which was neither designed nor presented to participants as a weight loss or weight control program. In addition to their own dietary health goals, many women enter the classes with multiple concerns stemming from their roles as caretakers. This often means balancing dietary preferences of family members that may be in direct conflict with the recommendations of the NEP. Classes are designed to provide a positive action-oriented view of the relationship between diet and health, and the importance of "caring for the caretaker".

The SRC intervention, grounded on a model of mindfulness-based stress reduction (53), is taught by masters-level psychologists having extensive training in both yoga and mindfulness meditation. Though attentionally equivalent to the NEP, the SRC contained neither formal didactic material in nutrition nor instruction in cooking. Women randomized to the usual care (UC) control condition received no formal intervention of the type given to SRC or NEP participants.

Measures: Data used in this report were obtained from self-report (mainly optically scannable) forms, medical chart review, and anthropometric measurement. Measures were made at baseline (just prior to the start of intervention or time-adjusted for women randomized to UC), 4 months (just after the intervention was completed), and 12 months. Data were collected on demographic and reproduction-related factors. Health history information included past and present medical/psychiatric history and treatment. A wide variety of psychological variables were measured using self-administered forms (54-64).

Assessment of dietary intake was made by the seven-day diet recall (7DDR) (65). The resulting nutrient intake report (66) was used to target problem areas in the diet. Body mass was measured at every clinic visit.

The factors investigated for their relationships to change in dietary factors and body mass can be grouped into demographic, medical, psychological, and intervention adherence. For the purposes of this report, class attendance is used as a measure of adherence to the NEP intervention protocol. A questionnaire regarding expectation of the anticipated helpfulness of the study arm into which the subject was randomized was asked of each participant. Three questions were asked of everyone, regardless of assignment: 1) whether they thought the group to which they were assigned made sense in terms of the approach to coping; 2) whether they thought they would recommend it to a friend; and 3) how much support they thought that they would receive. A fourth question was asked to individuals not randomized to control: whether they thought the specific intervention to which they were assigned would help.

Statistical Methods: Simple univariate statistics were computed to provide a description of the study population. As the main outcome variables in this study, change in dietary intake of relevant nutrients (fat (% energy), complex carbohydrates (g/d), dietary fiber (g/d)) and body mass (kg) were measured on a continuous scale. The values for both 4-month and 1-year outcomes were calculated as the follow-up measure minus the baseline level. Descriptive

analyses were performed to confirm that the assumptions of normality and homoskedasticity were not violated (67). To test the hypothesis that there was no association between treatment groups with respect to dietary intake and body mass at both 4-month and 1-year follow up, an analysis of variance (ANOVA) was conducted for each dependent variable using PROC GLM (68). Diagnostic statistics were run in order to test for model goodness of fit and to identify any outliers that would unduly influence the results of the ANOVA. In these models, treatment group was fit as a categorical variable, and the baseline value of the dependent variable was fit to control for regression to the mean. In the dietary outcome models social desirability was fit to control for possible bias in the self-report measures, as the 7DDR was previously shown to be subject to this bias, especially in women (69, 70). In addition, we examined the role of tamoxifen on dietary intake and change in body mass.

All dietary models were fit overall and for various subsets of the data based on baseline levels of psychological symptoms and expectation. Also, analyses were conducted within the NEP group to examine the relationship between class attendance and changes in dietary fat or body mass. Although the main focus of this report is on the effect of the intervention on diet-related variables, there was an interest in the role of diet in influencing psychological factors. Therefore, similar ANOVA models were fit with changes in: depression, self esteem, health-related quality of life, loneliness, and psychological distress as the dependent variables, in each instance controlling for baseline levels of the parameter.

RESULTS

In keeping with the rationale for conducting an RCT, it was not necessary to control for demographic and medical factors analytically in terms of testing the main effects of the intervention (as they were controlled by design). Demographic variables (table 1) indicated that participants in the study generally were well educated, married, predominantly white, and employed.

Results of the linear regression models used to examine changes in consumption of fat (% energy), complex carbohydrates (g/d), and dietary fiber (g/d) and body mass (kg) at 4 months (table 2) indicated large reductions in fat intake and body mass in the NEP versus either the SRC or UC. The women in the NEP returned to their baseline body mass at 12 months of follow up but continued to show a significant decrease in fat, and increases in carbohydrate and fiber intake. Besides the statistically significant differences noted in table 2, there were marginally significant ($0.05<p\leq0.10$) differences between the NEP and the SRC for complex carbohydrates at12 months and between the NEP and the UC for fiber at 4 months. There also was a suggestion of a difference between the NEP and SRC for fiber intake in the overall group at 12 months ($0.10<p\leq0.15$). Women in the NEP with higher-than-mean psychological distress, as assessed by the general symptom index (GSI) of the SCL-90 had a lower than average reduction in fat intake at 4 months, but tended to maintain their reduction to a greater extent at 12 months (the "High Symptoms" column in table 2, see figure 1 for a graphical depiction of this). Body mass reduction was smaller in this group at 4 months and the increase from baseline was higher at 12 months. In addition to results related to psychological distress, there were significant inverse relationships between 4-month change in fat intake (% energy) and change in both self esteem ($b = -0.08$, $p = 0.04$) and depression ($b = -0.03$, $p = 0.01$). However, there was no effect at 1-year for self-esteem or for depression. In the subset of women who had higher-than-average expectation of a beneficial effect of the intervention, there were larger reductions from baseline in energy as fat at 4 ($p<0.0001$) and 12 months ($p=0.0002$) and in body mass at 4 months ($p=0.002$) (see table 3 and figure 1). There also was a suggestion of a difference between the NEP and SRC for fiber intake in the high expectation group at both 4 and 12 months ($0.10<p\leq0.15$). Reduction in body mass was larger at 4 months, but returned to about the group average at 12 months. Women in the NEP with lower-than-average expectation had smaller reductions in energy as fat and body mass at 4 months and were less able to maintain the change out to 12 months. Expectation had no influence on these outcomes in the SRC or UC. This is in marked contrast to the changes in the high expectation subsample of subjects in the NEP in which the changes were much larger and significantly different from zero (except for the 0.16 kg increase from baseline weight at 12 months (table 3)).

In the NEP data subset, we examined the relation between class attendance as a marker for adherence and change in both fat intake and body mass (table 4). In this smaller group, statistical power is limited. However, we were able to fit class attendance in the GLM model and found that there was an suggestion of a reduction of about 0.43% energy as fat ($p=0.16$) and a marginally significant 0.22 kg decrease in body mass ($p=0.09$) at 4 months for each class attended. The effect of class attendance seemed to persist at 12 months. Also shown in table 4 are results based on class attendance for the subsets of women with higher-than-average baseline psychological symptoms and expectation.

Analyses stratified by tamoxifen use produced some interesting results. For women not on tamoxifen, the 4-month results were larger for those in the NEP (-6.39% energy, $p = 0.0002$) as opposed to women receiving tamoxifen (- 5.36% energy, $p = 0.005$). It appeared that weight loss for those women on tamoxifen was confined entirely to those in the NEP (-2.08 kg, versus a slight gain in the SRC and UC, $p = 0.003$). Results at 1-year reflected a proportional increase in both groups (a decrease of 4.53% energy from baseline in non-tamoxifen users versus 3.82% in users, both $p<0.05$).

DISCUSSION

The NEP resulted in improvements in dietary intake that were most pronounced at 4 months, but persisted at high levels to one year. This was observed even after statistical control for social desirability, a known bias of this type of dietary self-report data in populations of women (69, 70). Although this was not billed as a weight reduction trial, reduction in body mass and subsequent maintenance of the reduced mass is a logical concomitant of change in dietary fat intake (71). Our dietitian-led interventions are designed to maintain an isocaloric diet in subjects (71) though the initial enthusiasm for adopting a less calorie-dense diet often results in some weight loss. Despite a significant reduction in body mass at 4 months, it was not maintained at one year, an observation consistent with initial enthusiasm that could not be maintained. However, in certain subsets of the data, reductions were maintained.

Overall, these findings support the feasibility of assisting women with breast cancer in making significant dietary changes in a weekly 15-session group format. The intervention was of lower intensity than that used, for example, in the Ornish studies (26-29). In terms of intensity and level of participation required, it is comparable to the Women's Health Initiative dietary modification (DM) arm (72). Thus, it could be reproduced readily in many centers around the U.S.

One of the most interesting and potentially important findings is the effect of expectations in modifying the effect of the intervention. For the analyses of these data subsets, the statistical power was limited by the reduced sample size. Nevertheless, there appear to be effects of a much larger size in the subset of women who had above-average expectation in the potential effectiveness of the nutrition intervention. For example, they showed 4-month change at a somewhat higher level (-7.66% vs. -3.70% of energy as fat) than the women with lower expectation. The differences were even more striking at 12 months, with the decrease from baseline in the high expectation group being nearly triple that of the low expectancy group (-5.31% vs. -1.88% of energy as fat). Several methodological papers (73-75) have discussed the limitations of randomized controlled trials in testing interventions that are largely or wholly behavioral, in that the beliefs about the intervention could significantly modify the extent of active participation in the intervention. This finding of a significant level of effect-modification in this dietary intervention supports the concerns raised in the methodology papers and suggests that designs that examine self-selected arms in comparison to randomized arms may yield a fairer test of the interventions and at the same time provide a better estimate of real-world effectiveness. It is important that future investigations be designed for formal testing of the role of self-selection factors in modifying the effect of behavioral interventions such as the NEP. Given that such interventions could affect both the psychological and biological courses of early-stage breast cancer and that there is no treatment for these women once they have completed their relatively short-term conventional therapy, the results of such a trial would have great public health relevance.

The results in the subset of women with greater-than-average symptoms of distress (table 2) are interesting in this regard. In this group there were slightly smaller decreases in body mass and fat intake at 4 months, but much more of the change was maintained at 12 months. The severity of symptoms and the related issue of perceived vulnerability are known to influence the motivation of individuals to comply with dietary and other interventions (76-80). The success of the more distressed women in this study may be related to this. Moreover, the level of distress/psychological symptomology could be related to selection factors that also might

influence results in a trial where subjects are allowed to choose the NEP intervention as opposed to agreeing to accept random assignment.

While it is intuitively obvious that changes in self esteem would be inversely related to change in fat (i.e., it makes sense that as a woman is successful in decreasing her fat consumption while in the NEP, her self-esteem increases), the inverse association with change in depression at 4 months is not so easily interpreted. There is something that is clearly bothersome in terms of this inverse relation (i.e., as women are more successful in achieving the fat goal of the trial they are more depressed), and this may be related to the inability to maintain all of the change in the dietary variables or virtually any of the change in weight at 12 months of follow up. These women may have differed in perceived levels of compliance or had higher individual standards than others in the group. Those NEP women with higher-than-average depression at baseline appeared to have slighter higher-than-average reduction in fat intake at 4 months, but appeared to have maintained the change more poorly than the group as a whole. This also speaks to the relation between diet change and depression relative to issues around disappointment in one's ability to make and maintain change and for that change to result directly in improved psychological well-being. These findings are similar to those in the weight loss literature indicating that depression or other emotional distress seems to interfere with maintenance of weight loss (81, 82). It is worth noting that the average depression scores were well below cut-off scores for clinical depression, so it is unlikely that any initial changes would be indicative of the loss of appetite and weight loss that would characterize a higher level of depression.

APPLICATIONS

While this dietitian-led group approach appears successful in creating dietary change in breast cancer patients, several findings are relevant to placing this intervention in the context of real nutrition practice. First, a woman's distress at her perceived inability to comply with a dietary intervention (or a perception that weight loss is a desired end) could have a number of negative effects over time, both in demoralization that could lead to abandoning dietary efforts entirely, and in her feeling guilty over not doing all that is possible to contribute to her recovery, thereby reducing emotional quality of life. Thus, while the NEP may have potential emotional benefits in cancer patients, it is important to support long-term maintenance (e.g., some sort of follow-up) to sustain those potential benefits and prevent poorer emotional outcomes. In a commentary focusing on nutrition and quality of life with special reference to older patients, Schlettwein-Gsell (83) speculated on the potential psychosocial benefits associated with eating *per se*. For example, eating provides a source of pleasure and enjoyment, meals frequently offer the opportunity for socialization, and the ability to make healthful food choices may enhance self esteem, one of the few psychological variables that we observed to co-vary with dietary fat change in this study.

Second, the results of this study indicate that in making an intervention trial applicable to real life situations, basic issues of self-selection must be addressed. Even when interventions such as the NEP are found to be efficacious in an RCT, there is no guarantee that the observed effect would apply in real clinical practice. Likewise, a small or nonexistent effect in an RCT would not rule out a larger and more relevant effect under conditions in which patients actually receive treatment that they desire and have an active role in selecting. Although not designed as a rigorous test of such an interaction, the results from this trial strongly suggest that belief in the benefit of the NEP enhances the effect of that treatment and compliance with its prescription. Beyond the expectation of physical improvements through compliance, there are important psychological benefits that may be provided by a dietitian-led program such as the NEP to women who are actively searching for support during a time of great stress.

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Table 1. Characteristics of breast cancer patients at baseline (n=161), BRIDGES [a] Study, Worcester, MA, 1995-1998.

VARIABLE	n	%
Demographic:		
Education		
High School or Less	32	19.9
Some College	62	38.5
Bachelor Degree	28	17.4
Graduate School	39	24.2
Martial Status		
Single/Never Married	17	10.6
Married	112	69.6
Living with Partner	4	2.5
Separated	4	2.5
Divorced	17	10.6
Widowed	7	4.3
Race		
White	154	96
Other	7	4

Employment Status		
No	32	20
Full-time	95	59
Part-time	34	21
Menopausal Status		
Pre-menopausal	59	36.6
Post-menopausal	102	63.4
Disease & Treatment Related:		
Stage		
Stage I	91	57.0
Stage II	70	43.0
ER Status		
Positive	105	73.4
Negative	38	26.6
Tamoxifen Use		
Yes	67	43.8
No	86	56.2

Chemotherapy Use		
Yes	85	53.8
No	73	46.3
Radiation Use Before Study		
Yes	99	63.1
No	58	36.9
Radiation Use During Study		
Yes	21	13.38
No	136	86.62
Intervention Group:		
Usual Care	57	35.4
Nutrition	52	32.3
Stress Reduction	52	32.3

[a] BRIDGES, Breast Research Initiative for DeterminG Effective Skills.

Table 2. Adjusted (least squares) Mean [a] Change in Dietary Factors and Body Mass at 4 and 12 Months of Follow-Up, Overa for Women with Higher-Than-Average Symptoms, The BRIDGES Study, Worcester, MA 1995-1998.

Variable:	n	Baseline [b] Mean (SD)	Overall Group [c] 4 Month Mean (SE)	Overall Group [c] 12 Month Mean (SE)	High Symptoms (n=64) [c, d] 4 Month Mean (SE)	High Symptoms (n=64) [c, d] 12 Month Mean (SE)
Total Fat (% energy)						
Usual Care	54	33.5 (8.5)	0.32 (1.08)	-0.24 (1.07)	-1.07 (2.12)	-0.85 (1.54)
Nutrition Education	50	34.0 (8.6)	-6.07 (1.16) [x,y,z]	-4.17 (1.06) [x,y,z]	-5.69 (2.36) [x]	-4.60 (1.58) [x,y]
Stress Reduction	50	34.3 (7.4)	0.99 (1.09)	-0.06 (1.08)	-1.71 (2.42)	-1.98 (1.67)
Complex CHO (g/d)						
Usual Care	54	104.4 (42.5)	-6.02 (5.39)	2.95 (5.79)	-12.37 (7.52)	11.12 (12.09)
Nutrition Education	50	112.1 (53.4)	10.71 (5.82) [y]	8.00 (5.73)	11.56 (8.86) [y]	3.29 (13.00)
Stress Reduction	50	108.2 (37.0)	-1.69 (5.44)	-7.50 (5.85)	2.39 (8.10)	-1.16 (13.43)
Fiber (g/d)						
Usual Care	54	13.5 (5.4)	-0.23 (0.76)	0.23 (0.74)	-0.13 (1.15)	1.32 (1.29)
Nutrition Education	50	14.5 (7.2)	1.85 (0.82) [x]	1.47 (0.73) [x]	1.34 (1.33)	2.04 (1.37)
Stress Reduction	50	14.2 (6.3)	0.59 (0.76)	-0.14 (0.75)	2.83 (1.23) [x]	0.56 (1.43)
Body Mass (kg)						
Usual Care	56	74.0 (17.5)	0.14 (0.35)	-0.52 (0.60)	-0.15 (0.56)	0.06 (1.05)
Nutrition Education	50	70.9 (11.8)	-1.34 (0.37) [x,y,z]	0.33 (0.59)	-1.08 (0.70)	0.59 (1.15)
Stress Reduction	52	72.0 (13.7)	0.02 (0.35)	0.81 (0.58)	-0.86 (0.62)	0.42 (1.14)

[a] Values shown are based on self reports of dietary intake of total fat (% of energy), complex carbohydrates (CHO) (g/d), and fiber (g/d) and measured body mass. Change scores are adjusted statistically for baseline value, using the General Linear Models procedure in SAS. Models based on dietary factors also controlled for social desirability score, which was significantly associated for the 4-month total fat results overall and for

women with high expectation.

[b] For baseline values, which show the mean and standard deviation for each variable, there were no differences between intervention categories.

[c] Values shown are the mean and standard error for fat, complex carbohydrates (CHO), fiber, and body mass.

[d] This analysis is stratified to include only those subjects with above-average symptoms of distress at baseline based on the GSI of the SCL-90.

[x] Indicates that the difference (change from baseline) differs from zero ($p \leq 0.05$).

[y] Indicates that the nutrition intervention is different from the individual choice ($p \leq 0.05$).

[z] Indicates that the nutrition intervention is different from stress reduction ($p \leq 0.05$).

Table 3. Adjusted (least squares) Mean [a] Change in Dietary Factors and Body Mass at 4 and 12 Months of Follow-Up, Comp with Higher- and Lower-Than-Average Expectation of a Beneficial Result, The BRIDGES Study, Worcester, MA 1995-1998.

Variable:	n	High Expectation (n=87) [b, c] 4 Month Mean (SE)	High Expectation (n=87) [b, c] 12 Month Mean (SE)	Low Expectation (n=71) [b, d] 4 Month Mean (SE)	Low Expectation (n=71) [b, d] 12 Month Mean (SE)
Total Fat (% energy)					
Usual Care	54	0.74 (1.42)	-0.35 (1.50)	0.03 (1.63)	0.80 (1.49)
Nutrition Education	50	-7.66 (1.49) [x,y,z]	-5.31 (1.36) [x,y,z]	-3.70 (1.87) [z]	-1.88 (1.71)
Stress Reduction	50	0.14 (1.51)	-0.29 (1.57)	1.84 (1.58)	-0.08 (1.45)
Complex CHO (g/d)					
Usual Care	54	1.61 (8.14)	7.78 (9.00)	-14.81 (5.97) [x]	-1.82 (7.08)
Nutrition Education	50	11.4 (8.47)	12.01 (8.17)	7.23 (6.84) [y]	1.08 (8.11)
Stress Reduction	50	1.74 (8.63)	1.22 (9.43)	-5.84 (5.85)	-13.71 (6.97)
Fiber (g/d)					
Usual Care	54	0.37 (1.15)	0.99 (1.20)	-0.97 (0.90)	-0.51 (0.79)
Nutrition Education	50	2.69 (1.19) [x]	2.67 (1.09) [x]	0.87 (1.03)	-0.26 (0.90)
Stress Reduction	50	0.20 (1.22)	0.10 (1.26)	0.56 (0.88)	-0.24 (0.78)
Body Mass (kg)					
Usual Care	56	0.40 (0.48)	0.98 (0.77)	-0.29 (0.49)	-0.54 (0.88)
Nutrition Education	50	-1.58 (0.50) [x,y,z]	0.16 (0.69)	-0.90 (0.57)	0.43 (0.99)
Stress Reduction	52	0.31 (0.50)	0.66 (0.75)	-0.39 (0.49)	0.84 (0.84)

[a] Values shown are based on self reports of dietary intake of total fat (% of energy), complex carbohydrates (CHO) (g/d), and fiber (g/d) and measured body mass. Change scores are adjusted statistically for baseline value, using the General Linear Models procedure in SAS. Models based on dietary factors also controlled for social desirability score, which was significantly associated for the 4-month total fat results overall and for

women with high expectation.

[b] Values shown are the mean and standard error for fat, complex carbohydrates (CHO), fiber, and body mass.

[c] This analysis is stratified to include only those subjects with above-average expectation of a favorable outcome due to their randomization condition at study baseline. Note that the number shown is based on all subjects with expectation data at baseline. This will exceed the total for all subsets, due to missing data.

[d] This analysis is stratified to include only those subjects with above-average expectation of a favorable outcome due to their randomization condition at study baseline. Note that the number shown is based on all subjects with data on expectation at baseline. This will exceed the total for all subsets, due to missing data.

[x] Indicates that the difference (change from baseline) differs from zero ($p \leq 0.05$).

[y] Indicates that the nutrition intervention is different from the individual choice ($p \leq 0.05$).

[z] Indicates that the nutrition intervention is different from stress reduction ($p \leq 0.05$).

Table 4. Effect of Class Attendance in the Nutrition Education Program (NEP), on Change in Selected Study Outcomes. The BRIDGES Study, Worcester, MA 1995-1998.[a]

	Overall [b] (n=52)		High Symptoms [b, c] (n=19)		High Expectancy [b, d] (n=32)	
	4 Month	**12 Month**	**4 Month**	**12 Month**	**4 Month**	**12 Month**
Total Fat (% energy)	-0.43 (0.28)	-0.42 (0.30)	-0.65 (0.55)	-0.78 (0.52)	-0.48 (0.31)	-0.31 (0.41)
Complex CHO (g/d)	0.36 (1.72)	0.80 (1.23)	-0.17 (3.35)	1.25 (2.85)	0.09 (2.31)	-0.29 (1.70)
Fiber (g/d)	0.03 (0.24)	0.15 (0.19)	-0.12 (0.48)	-0.09 (0.37)	-0.15 (0.30)	0.05 (0.25)
Body Mass (kg)	-0.22 (0.13)	-0.23 (0.15)	0.07 (0.25)	0.35 (0.21)	-0.24 (0.17)	-0.23 (0.20)

[a] Values shown represent the effect per class based on the linear regression model obtained from Proc GLM controlling for baseline value. For the models based on dietary fat, we also controlled for social desirability score. Due to small sample sizes, no result was significant at p=0.05.

[b] Values shown are the mean and (standard error) for fat, complex carbohydrates (CHO), fiber, and body mass.

[c] This analysis is stratified to include only those subjects with above-average symptoms of distress based on the GSI of the SCL-90.

[d] This analysis is stratified to include only those subjects with above-average expectation of a favorable outcome due to their randomization condition.

A Meditation-Based Stress Reduction Intervention for Women with Breast Cancer:

Psychosocial Outcomes and 1- Year Follow-Up

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INTRODUCTION

The challenges facing women coping with the diagnosis of breast cancer and its treatment are daunting and have been well-described in previous research (*1, 2*). The nature and extent of the emotional impact of this process varies extensively across individuals, and has been shown to be influenced by social support (*3*), age (*4*), coping style (*5*) and temperament (*6*), and aspects of medical treatment (*7, 8*). Depressive symptoms have been frequently observed in these women (*5, 9*) as have fears about the future, and other aspects of quality of life (*10*). Generally, much of this distress improves gradually over time (*11, 12*), though there are specific areas of distress that may be more enduring (e.g., fatigue, intrusive thoughts about the cancer diagnosis or treatment).

In an effort to assist women in the process of coping with breast cancer, a number of different psychosocial interventions have been devised (*13*). Some interventions have focused on providing long-term emotional support and promoting emotional expression and communication with loved-ones for women with advanced or recurrent disease (*14-16*). A number of other interventions have used briefer, more educationally focused groups for cancer patients with earlier-stage disease (*17, 18*), a format that may be more appropriate to their needs (*13*). The programs often have consisted of different combinations of education about their disease, treatment, and needs for ongoing screening, cognitive stress management and problem-solving techniques, an opportunity for mutual support, as well as some formal practice with relaxation techniques.

A wide variety of intervention packages have been tested and have shown positive benefits to cancer patients in general and to breast cancer patients specifically, as measured by psychosocial endpoints (*13, 19*), as well as immune system function and survival (*17, 20*). However, relatively few have used control conditions, and most of these have used no-treatment or standard care controls . From most of the studies to date, it has been difficult to move research forward regarding identifying specific components of treatment which are essential to the improvements found, or for whom the particular interventions may work best. In order to answer those questions, an essential step is devising an appropriate comparison condition, which would control for contact time, elements of group support, expectations of help, and general credibility. Helgeson and colleagues, in a recent line of research, have shown the most consistent benefit to women with early-stage breast cancer from relatively brief, psycho-educational interventions (vs. support-group formats, which are the most common though least well-tested interventions in community-based programs) (*21, 22*).

Our goal in this 3-armed randomized controlled trial was to study the specific effects of a meditation-based psycho-educational program for women with early-stage breast cancer, as compared to a standard care control as well as a group nutrition intervention that provided equivalent contact time, elements of group support, plausible expectations that the intervention may be helpful in some way, and general credibility and acceptance by patients.

METHODS

Research Participants: The Breast Research Initiative for DeterminiG Effective Strategies (BRIDGES) for Coping with Breast Cancer was an randomized controlled trial into which 178 women with breast cancer were enrolled from four hospital-based breast clinics in southern New England over a 2-year interval. The hospitals draw patients representative of the general population in the region: one is the principal academic hospital of a medical school; one is a community hospital with some university affiliation, and a third is the hospital of a staff-model HMO. The fourth hospital is one of several teaching/community hospitals in Providence, R. I..

Eligibility: Women eligible to be in this study were those who: 1) were newly diagnosed (within two years) with stage I or II cancer of the breast; 2) were between 20 and 64 years of age; 3) were capable of understanding informed consent in English (i.e., they had to have a working knowledge of English and be

judged to be compos mentis); 4) had a working telephone and were willing to be contacted at home for dietary and psychosocial assessments; 5) were planning to remain in the study area for at least two years following recruitment; 6) were Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2 (i.e., able to function normally >50% of the time); and 7) were willing to accept randomization. Specific exclusion criteria included: 1) a previous diagnosis of cancer in the past five years, except non-melanoma skin cancer; 2) current chronic substance abuse (either drug or alcohol, e.g., >3 drinks per day more than 3 days per week); and 3) past or present major psychiatric or neurological disorder that would preclude or severely limit participation in the study (e.g., severe major depression, schizophrenia, organic brain syndrome, psychosis, or significant cognitive impairment).

Randomization: Once enrolled, women were randomized into one of three study conditions: 1) A mindfulness meditation-based stress reduction program that used the U. Mass. Medical School's Stress Reduction Clinic Program (*23*) as its centerpiece (SRC); 2) An intensive dietary intervention known as the Nutrition Education Program (NEP); or 3) Usual supportive care (UC) also described to the participants as "Individual Choice". The interventions were conducted at a single site in Worcester, MA. Randomization was blocked by study site, age ($< \text{or} \geq 50$ years of age), and stage of disease.

Measures: Data collected for use in this report were obtained from self-report using paper and pencil (mainly optically scannable) forms, telephone interview, medical chart review, and anthropometric measurement. Measures were made at baseline (after randomization and just prior to the start of the intervention or time-adjusted for women randomized to UC), 4 months (just after the intervention was completed), and 12 months.

Demographic and reproduction-related historical data were collected for each participant, including the following: age, gender, marital status, education, number of children, number and dates of pregnancies, breast feeding, current menopausal status at the time of diagnosis (including surgical menopause), and oral contraceptive use. Disease and treatment-related data collected through chart review included the following: date of initial diagnosis; pathology (including histological type and grade); stage (TNM classification), estrogen receptor status, treatment modalities used (i.e., chemotherapy, radiation, type of surgery, hormonal treatment), and ECOG performance status. Health history information included past and present medical/psychiatric history and treatment (including history of exposure to estrogens, unusual menstrual problems). Interval data collected from a chart review or interviews included: current medications; chemotherapy; radiation; surgery; other lab work (clinical chemistries, hematology, etc.); clinical events; and disease events (e.g., infection or other treatment-related complications, local/regional or metastatic recurrence of disease).

Psychosocial variables included standardized and validated self-report questionnaire measures emotional well-being, including the following: anxiety (Beck Anxiety Inventory (*24*)); depression (Beck Depression Inventory (*25*)); subjective social support (UCLA Loneliness Scale (*26*)); self-esteem (Rosenberg Self-Esteem Scale (*27*)); and general psychological distress with the Symptom Checklist 90-Revised (SCL-90-R (*28*)). Coping and other personality measures included the following scales: Dealing with Illness (*29*); the short form of the Mental Adjustment to Cancer scale (Mini-MAC (*30*)); Sense of Coherence (SOC (*31*); and Courtauld Emotional Control Scale (CECS) (*32*).

Quality of Life was measured by self-report using the Functional Assessment of Cancer Therapy-Breast Cancer form (FACT-B (*33*)) using the general cancer items, breast cancer-specific items, and additional spirituality items. Assessment of dietary fat intake and change over time was made by the seven-day dietary recall measure (7DDR) (*34*). Body mass was measured at every clinic visit.

Expectations regarding the anticipated helpfulness of the intervention arm into which the women were randomized was measured by self report using four items, each rated on a 5-point Likert scale. Other process measures included attendance at group sessions.

Participants received monthly telephone calls intended to assess their general sense of well-being, gather information on any lifestyle changes they may have undertaken on their own, monitor the use of community support services, and provide them with an opportunity to request assistance in accessing services (including referral for counseling).

Interventions: The women randomized into the two active intervention arms were allowed some latitude in choosing the timing of their participation in the intervention program. That is, cycles of the intervention groups were run three times per year, and participants could choose any of the cycles beginning in the year following randomization.

Stress Reduction: The stress reduction intervention (SRC) is built around the structure of a long-standing program based at the University of Massachusetts Medical School, an eight-week course designed to assist patients with a wide range of chronic medical conditions. Patients attend 2.5 hour-long classes in groups of 25 - 30 once a week, with an eight-hour intensive retreat session on a Saturday in week 6 (*23, 35*). The program is based on intensive training in a meditative discipline known as mindfulness, which is often described as the core of Buddhist meditative practice. Mindfulness can be defined most simply as the intentional maintenance of a non-judgmental, non-reactive moment-to-moment awareness and the systematic re-establishing of that awareness when it dissipates, mastery of which is typically developed through meditative practice. These skills are taught in the program through a combination of sitting meditation, a guided body-scan approach to relaxation, and gentle yoga (in session and through home practice guided by 45-minute audiotapes). These elements are combined with didactic material on the physiology of stress, as well as with cognitive-behavioral techniques including self-monitoring of pleasant events and stressors, and role-playing around communication and coping with adversity. The appearance is a highly interactive and educational rather than psychotherapeutic.

In addition to the standard SRC program, we added two 2-hour introductory small psychoeducational group sessions only for women with breast cancer from this study, with more focus on mutual support and issues specific to coping with the emotional impact of breast cancer diagnosis and treatment. We also added four weekly 2-hour booster sessions in the same small group format at the end of the SRC program. These groups were used to continue meditation practice as well as to further address the breast-cancer-specific issues involved in getting on with life after going through breast cancer. All six of these groups were led by a female psychiatrist, with experience with meditation and issues in coping with cancer. Besides the group sessions, this intervention included two one-hour individual meetings with a stress reduction instructor, one just before and one just after the regular SRC program.

Nutrition Education Program: The Nutrition Education Program (NEP), implemented by registered dietitians, used intervention strategies based on the principles of social cognitive theory (*36*) and patient-centered counseling for negotiating health behavior change (*37*). The NEP was constructed to be roughly equivalent in terms of intensity and contact time to the SRC condition. It includes a total of 14 weekly 2½ hour group sessions and one longer "Gourmet Event" session on a weekend day. Groups are made up of approximately 8-10 women with breast cancer and include only women in this intervention study In addition, individual sessions with the program nutritionist were scheduled before starting and after completing the group program. The primary objectives of the NEP are to : 1) increase patient awareness of dietary risk factors associated with breast cancer; 2) increase patient knowledge of nutrition; 3) increase patient confidence (i.e., self-efficacy) in her ability to make dietary changes, 4) enhance patient behavioral and cognitive skills for adherence to a low-fat, high fiber plan for eating; and 5) provide group support in making dietary changes.

While keeping fat and fiber as the main focus, a variety of topics are discussed during the group sessions. Topics include: vitamins, minerals, vegetarian meals, functional constituents such as indoles, and phytoestrogens, caffeine, alcohol, herbs and spices. Teaching techniques include didactic presentations and group discussion, hands-on label reading and healthy food preparation in session, field trips, and presentations

on ethnic foods. Additional program content focuses on the process of making and maintaining behavior change, including stages of behavior change, time management, menu planning, and problem-solving around work/family schedules and food preferences. The NEP was neither designed nor presented to participants as a weight loss or weight control program.

Usual Care: Women randomized to the usual care (UC) receive no formal intervention of the type given to SRC or NEP participants. There is no restriction on their participation in support groups and any other community-based services, though they do agree to refrain from taking the U. Mass Stress Reduction Clinic Program on their own.

Statistical Methods: Simple univariate statistics were computed to provide a description of the study population. As the main outcome variables in this study, change in psychosocial variables were measured on a continuous scale, the values for both 4-month and 1-year outcomes were calculated as the follow-up measure minus the baseline level. Descriptive analyses were performed to confirm that the assumptions of normality and homoskedasticity were not violated (*38*). To test the hypothesis that there was no association between treatment groups with respect to psychosocial variables at both 4-month and 1-year follow up, an analysis of variance (ANOVA) was conducted for each dependent variable using PROC GLM (*39*). Diagnostic statistics were run in order to test for model goodness of fit and to identify any outliers that would unduly influence the results of the ANOVA. In these models, treatment group was fit as a categorical variable and the baseline value of the dependent variable was fit to control for regression to the mean. In addition, we examined the changes in scores for the subsets of women with higher-than-average baseline Beck Depression Inventory scores and with higher than median expectation of benefit from their group.

RESULTS:

A total of 178 women were recruited from the four practice sites. Some initial attrition either before or after randomization (highest at the most distant site) led to a total of 162 women in the three groups. Retention from the point of completing baseline questionnaires has been roughly 90% to the 12-month data collection point.

Demographic variables (summarized in Table 1) indicated that participants overall were well educated, married, predominantly white, and employed. Besides the factors on which we randomized (practice site, disease stage, and age), there were no differences between groups on a host of other important potential confounders such as medical treatment, menopausal status, education, employment, or race (Table 2).

Despite being essentially balanced for the demographic and disease-related variables, some of the baseline psychosocial measures approached significance between groups. To control for these baseline differences, analyses were conducted using baseline value-adjusted change scores.

The change scores on the psychosocial measures from baseline to 4-month and 12-month intervals (adjusted for individual baseline scores) were compared, by group, using analysis of variance (PROC GLM) and their significance levels are summarized in Table 3. Generally, the SRC group showed the greatest improvement (a higher level of adjusted change from baseline) on psychosocial measures at 4 months and 12 months.

Four-month Results: Significant differences were found favoring the SRC over both the UC and NEP at four months on SCL-90-R scores including the General Severity Index and the depression subscale. For the interpersonal sensitivity and hostility subscales, there were significant differences between the SRC and the NEP and UC, respectively. The SRC group showed increases in levels of active-cognitive coping, with the difference being significantly different from UC (as was the NEP difference). SRC women also showed a larger decrease in level of overall emotional over-control on the CECS at 4 months in comparison to either the NEP or UC. The FACT-B quality of life measure showed significant advantages of the SRC group vs. both the NEP

and UC on the Spirituality- Additional scale. The SRC group showed significantly reduced depression and helpless-hopeless thinking (using the BDI) compared to the NEP group.

The overall pattern that appeared at 4 months was that the SRC was doing best, followed by NEP, with UC doing least well. However, the NEP scores were significantly higher than the UC on only one psychosocial measure, Active-Cognitive Coping. Though a detailed report of the outcomes of dietary measures is reported elsewhere (*40*) and will not be repeated here. It is of note that only the NEP group had any significant changes from baseline in the direction of reducing the percentage of dietary fat, improving other dietary factors, and reducing body mass index from baseline to 4 months.

Twelve-month Results: At twelve months, the SRC continued to show a significant advantage over the other groups on several of the psychosocial measures. These include the Spirituality-Additional scale, and the Active-Behavioral Coping on the DWI scale (in comparison to UC).

Consistent with the patterns in the 4-month data, the NEP group showed intermediate results between the SRC and UC groups, on variables such as interpersonal sensitivity, active cognitive coping, and SCL-90-R hostility. However, in contrast to the 4-month results, the 12-month data showed the NEP group to be doing somewhat less well than the UC and SRC groups on certain variables. Of interest, it appears that NEP women increased their fat consumption slightly between the 4-month and 12-month measurement points and their weights returned to baseline levels.

Subset Analyses: To explore subsets of the sample who were hypothesized to have a differential response to the interventions, two subsets of women were identified. The first was a group of women whose Beck Depression Inventory scores were above the average for this group at baseline. The second was to look at the issue of expectancy, examining those women who believed (above the average level) that their intervention (determined by randomization) would be helpful to them. Analyses of variance for group differences were done for the psychosocial variables on these two subsets of patients.

Higher Baseline Depression: Among the women whose baseline Beck Depression scores were above the median, those in the SRC appeared to benefit on a wide variety of psychosocial measures at 4 months and 12 months. The results are summarized in Table 3. After 12 months, the SRC group was higher on active behavioral coping on the Dealing with Illness scale and higher on active cognitive coping at 4 months (than the UC women). There was also less Helpless/hopeless coping on the MAC. Regarding emotional distress, the SRC group of the subset reported less distress on the overall GSI at 4 months and three subscales of the SCL-90-R. Emotional quality of life appeared to improve only the SRC group and the Spirituality-Additional scale also favored the SRC group among women with higher baseline distress (significantly between the SRC and both the UC and NEP at 4 months and between the SRC and NEP at 12 months).

Higher Expectation of Help: Among women who reported above-average expectation in the effectiveness of the intervention to which they were randomized results also are summarized in Table 3. In general, among women who believed in the usefulness of the intervention to which they were randomized, there was considerably less advantage seen for the SRC. Indeed, none of the psychosocial measures in this subset showed significant advantages of the SRC over other groups over time. This is consistent with the results on melatonin (results in progress and submitted as an appendix to this grant application as well) and with the orientation taught in the SRC, which relates to being open to one's experience just as it is, without expecting or trying to 'make something' happen.

DISCUSSION:

These results show a significant beneficial effect of a meditation-based stress reduction/ psychosocial intervention on psychosocial measures, when compared to a credible educational attention placebo and a usual care control. The effects were somewhat less robust at 12 months than at the conclusion of treatment at 4-months. This finding is in contrast to some briefer (6-week) psychoeducational intervention studies with cancer

patients (*17*) where intervention effects have been found to be stronger at one year than immediately post-treatment.

The credibility of the nutrition education program (NEP) is validated by the fact that in that group (unlike the other two groups) women reduced their mean consumption of fat and actually lost weight (> 1 kg over the 4 months of intervention). The fact that the NEP group produced significant effects over the UC group on social support and active cognitive coping suggests that the NEP served as an effective placebo control condition in providing group support and a sense that the women were engaged in an activity that might improve their well-being. One of the more interesting findings was that of discovering a decrement in the emotional well-being of women in the NEP group overall. One hypothesis to explain this finding is that the women in the NEP were aware of the dietary changes that may be desirable, but had experienced difficulty in sustaining those changes over the 12-month time interval, as may be indicated by the rebound in percentage of calories from fat and return to their baseline body mass index at 12 months. Thus the apparent increases seen in their depression, general distress, and fatalism and reductions in emotional quality of life scores may be accounted for by a disappointment factor, following the inability of many of these women to sustain their dietary adherence. Because the data were collected contemporaneously, however, it is impossible to discern what may have come first.

The results of the subset analyses are particularly interesting in considering the translation of such intervention programs into the broader clinical setting. Though women in the SRC overall did best on several psychosocial dimensions, women with above-average baseline depression showed more consistent improvement and with more enduring differential effects. Even though the average was well below clinical cutoff scores, the women reporting somewhat higher distress at baseline seemed to respond particularly well to an intervention targeting psychosocial issues.

Also of interest is our examination of the effects of expectancy on emotional well-being effects of the groups. It is interesting to note that more women randomized into the NEP group believed strongly in the potential benefit of the intervention than did women in the other two groups. It makes sense that if a substantial number of women believe that nutrition could play an important role in their vulnerability to a disease recurrence, and that they had made those changes, that it may have a beneficial effect on their emotional well-being. This speaks to the importance of directly studying the effects of expectation as an effect modifier. It has recently been raised in the literature on research methodology that randomized controlled trials have severe limitations when the interventions are partly or wholly behavioral (*41-43*), in that belief in the different interventions may profoundly affect the level of active participation and enthusiasm for the intervention. This potential effect modification cannot be controlled out in the RCT, but must be examined in studies comparing randomized with self-selected participants in identical interventions.

This study is the first to quantify the specific effects of a psychosocial intervention in a design that controls for elements of group support, credibility of the comparison condition, and contact time. There seem to be specific effects of this intervention on self-report of depression, spirituality and emotional quality of life, and active-behavioral coping that endure at 12 month follow-up. Further study is needed to validate these results and particularly to explore the issue of which interventions will do best for which women. The population of women with breast cancer is very large and diverse and efforts to identify which women will be helped most by specific interventions will help move psychosocial interventions into the mainstream of breast cancer care.

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Table 1. Characteristics of breast cancer patients at baseline (n=161), BRIDGES[1] Study, Worcester, MA, 1995-1998.

VARIABLE	n	%
Demographic:		
Education		
High School or Less	32	19.9
Some College	62	38.5
Bachelor Degree	28	17.4
Graduate School	39	24.2
Martial Status		
Single/Never Married	17	10.6
Married	112	69.6
Living with Partner	4	2.5
Separated	4	2.5
Divorced	17	10.6
Widowed	7	4.3
Race		
White	154	96
Other	7	4
Employment Status		
No	32	20
Full-time	95	59
Part-time	34	21
Menopausal Status		
Pre-menopausal	59	36.6
Post-menopausal	102	63.4
Disease & Treatment Related:		
Stage		
Stage I	91	57.0
Stage II	70	43.0
ER Status		
Positive	105	73.4
Negative	38	26.6
Tamoxifen Use		
Yes	67	43.8
No	86	56.2

Chemotherapy Use		
Yes	85	53.8
No	73	46.3
Radiation Use Before Study		
Yes	99	63.1
No	58	36.9
Radiation Use During Study		
Yes	21	13.38
No	136	86.62
INTERVENTION GROUP:		
Individual	57	35.4
Nutrition	52	32.3
Stress Reduction	52	32.3
INSTITUTION:		
Fallon Medical	39	18.0
Memorial Health	46	28.6
R.I. Hospital	13	8.1
UMass Medical	73	45.3

[1] BRIDGES, Breast Research Initiative for DeterminG Effective Skills.

Table 2. Percentage of Patients in Various Demographic and Disease-Related Categories, by Practice Site, BRIDGES Study, Worcester, MA, 1995-1998.

	UMMS (n=73)	Memorial (n=46)	Fallon (n=29)	Miriam (n=13)	p-value
Stage I	54.8	50.0	75.9	56.2	0.12
Chemotherapy	47.1	69.6	48.3	46.2	0.09
Surgical Status					
Lumpectomy	76.1	80.4	78.6	38.5	0.02
Mastectomy	23.9	19.6	21.4	61.5	
Marital Status					0.12
Single	9.6	8.7	20.7	---	
Married	68.5	65.2	79.3	69.2	
Separated/Divorced/Widowed	21.9	26.1	---	30.8	
Race					
White	95.9	95.7	96.6	92.3	0.06
Education					
High School	13.7	23.9	37.9	---	0.03
Some College	43.8	41.3	31.0	15.4	
College +	42.5	34.8	31.1	84.6	
Employed					
Full-time	68.5	52.2	62.1	23.1	.06
Pre-Menopausal	43.8	32.6	20.7	46.2	0.13

[1] Based on the chi-square test unless any cell contained 5 or fewer observations

Table 3. Adjusted (least squares) Mean[1] Change of Psychosocial Outcomes at 4 and 12 Months after the Interventions, The BRIDGES Study, Worcester, MA 1995-1998.

		Baseline	Overall Group[2]		Higher Beck D (n=64)[2,4]		Higher Expectation (n=87)[2,4]	
	n	Mean (SD) [3]	4 Month	12 Month	4 Month	12 Month	4 Month	12 Month
Dealing With Illness/Act Behavioral								
Individual Choice	57	58.89 (9.20)	-0.82 (.85)	-3.08 (.93)[8]	-0.48 (1.14)	-2.34 (1.26)	-0.59 (1.24)	-2.83 (1.21)[8]
Nutrition	51	61.80 (9.46)	0.93 (.91)	-0.86 (.91)	1.14 (1.20)	0.27 (1.19)	2.17 (1.23)	0.03 (1.05)
Stress Reduction	52	63.2 (10.39)	-0.15 (.88)	-0.20 (.94)[5]	1.10 (1.10)	1.35 (1.13)[5]	-1.03 (1.30)	-1.03 (1.19)
Dealing With Illness /Act-Cognitive								
Individual Choice	57	61.02 (7.97)	-1.78 (0.64)[8]	-2.35 (0.83)[8]	-1.40 (0.82)	-1.57 (1.12)	-0.55 (0.86)	-2.11 (0.16)
Nutrition	51	61.43 (7.16)	0.70 (0.69)[7]	-1.44 (0.82)	0.76 (0.86)	-0.46 (1.06)	1.41 (0.86)	-1.54 (1.01)
Stress Reduction	52	62.06 (8.08)	1.52 (0.67)[5, 8]	-0.55 (0.84)	1.29 (0.79)[5]	-0.28 (1.01)	1.70 (0.90)	0.21 (1.13)
FACT-B								
Individual	57	117.26 (12.98)	-0.57 (1.42)	4.16 (1.44)[8]	-0.44 (2.07)	5.94 (2.09)[8]	-1.90 (1.95)	4.82 (2.31)[8]
Nutrition	51	115.88 (14.68)	-0.78 (1.52)	1.63 (1.41)	-0.94 (2.17)	2.48 (1.98)	0.38 (1.94)	2.57 (1.98)
Stress Reduction	51	113.90 (17.35)	2.12 (1.46)	3.38 (1.44)[8]	3.28 (2.01)	4.96 (1.96)[8]	-2.04 (2.04)	0.61 (2.19)
FACT-G/Emotion								
Individual	57	16.98 (2.48)	-0.09 (0.29)	1.02 (0.25)	0.08 (0.41)	1.66 (0.38)[8]	-0.91(0.44)[8]	0.76 (0.05)[8]
Nutrition	51	17.10 (2.5)	-0.13 (0.31)	0.16 (0.25)	-0.16 (0.43)	0.48 (0.37)	-0.35 (0.43)	0.05 (0.31)
Stress	52	16.17 (3.25)	0.56 (0.30)	0.70 (0.25)[8]	0.89 (0.40)[8]	1.07 (0.37)[8]	-0.28 (0.46)	0.61 (0.35)
FACT/Spirituality Subscale								
Individual Choice	57	20.33 (5.41)	0.40 (1.07)	-0.03 (0.53)	0.68 (1.72)	0.01 (0.77)	0.37 (1.89)	-0.17 (0.82)
Nutrition	51	19.75(5.24)	1.51 (1.15)	-0.25 (0.53)	2.90 (1.81)	0.37 (0.74)	2.13 (1.89)	-0.78 (0.72)
Stress Reduction	52	18.87 (6.12)	1.83 (1.11)	1.21(0.53)[6, 8]	1.63 (1.68)	1.65 (0.73)[8]	0.91 (1.98)	0.38 (0.80)

Sprituality - Additional								
Individual Choice	54	7.76 (2.17)	-0.10 (0.28)	0.09 (0.31)	-0.08 (0.40)	0.23 (0.43)	0.26 (0.41)	0.18 (0.44)
Nutrition	46	7.89 (2.92)	-0.54 (0.31)	-0.31 (0.31)	-0.53 (0.42)	-0.23 (0.41)	-0.66 (0.44)	-0.22 (0.42)
Stress Reduction	52	7.77 (2.72)	1.04 (0.29) [5,6,8]	0.93 (0.30) [5, 6, 8]	1.24 (0.38) [5,6,8]	1.08 (0.39) [6,8]	0.80 (0.44) [6]	0.75 (0.43)
BeckD[9]								
Individual Choice	57	1.38 (1.40)	-0.25 (0.18)	-0.35 (0.20)	-0.42 (0.19) [8]	-0.43 (0.25)	-0.50 (0.24) [8]	-0.37 (0.31)
Nutrition	51	1.47 (1.15)	0.09 (0.19)	-0.24 (0.20)	-0.11 (0.20)	-0.44 (0.23)	0.15 (0.24)	-0.20 (0.27)
Stress Reduction	52	1.71 (0.97)	-0.64 (0.18) [6, 8]	-0.59 (0.20) [8]	-0.88 (0.19) [6,8]	-0.92 (0.23) [8]	-0.37 (0.25)	-0.52 (0.30)
MiniMac/Fatalism								
Individual Choice	56	15.64 (2.35)	0.25 (0.22)	0.09 (0.24)	0.45 (0.28)	-0.15 (0.26)	0.43 (0.30)	0.003 (0.36)
Nutrition	51	14.86 (2.21)	0.26 (0.23)	0.45 (0.24) [8]	0.51 (0.28)	0.18 (0.26)	-0.10 (0.30)	0.27 (0.31)
Stress Reduction	51	15.69 (2.58)	0.50 (0.23) [8]	-0.03 (0.24)	0.41 (0.26)	-0.65 (0.25)	0.46 (0.32)	-0.25 (0.35)
MiniMac/Fighting Spirit								
Individual Choice	57	13.37 (1.68)	-0.27 (0.21)	-0.18 (0.21)	-0.12 (0.27)	-0.15 (0.26)	-0.39 (0.28)	-0.28 (0.31)
Nutrition	50	12.94 (1.97)	-0.144 (0.23)	0.07 (0.21)	-0.38 (0.29)	0.18 (0.26)	0.21 (0.29)	0.14 (0.29)
Stress Reduction	51	13.18 (1.88)	-0.06 (0.22)	0.72 (0.21) [6, 8]	-0.17 (0.27)	-0.65 (0.25) [6,8]	-0.06 (0.30)	-0.47 (0.32)
Helplessness/Hopelessness								
Individual Choice	56	10.39 (2.83)	0.46 (0.35)	0.20 (0.37)	0.78 (0.53)	-0.21 (0.51)	0.77 (0.46)	1.05 (0.58)
Nutrition	51	10.65 (3.12)	0.85 (0.38) [8]	0.91 (0.36) [8]	0.80 (0.55)	0.67 (0.48)	1.01 (0.47) [8]	0.81 (0.51)
Stress Reduction	51	11.33 (3.50)	-0.23 (0.37) [6]	-0.14 (0.37) [6]	-0.25 (0.51)	-0.17 (0.47)	0.81 (0.49)	-0.09 (0.56)
UCLA/loneliness Social Support								
Individual Choice	57	7.42 (1.89)	0.05 (0.20)	-0.42 (0.24)	-0.06 (0.28)	-0.60 (0.34)	-0.07 (0.25)	-0.71 (0.29) [8]
Nutrition	50	7.44 (2.23)	0.54 (0.22) [8]	0.26 (0.24) [7]	0.75 (0.30) [7,8]	0.41 (0.34) [7]	0.18 (0.25)	-0.03 (0.26)
Stress Reduction	51	7.39 (2.26)	0.18 (0.21)	-0.18 (0.24)	-0.29 (0.29) [6]	-0.37 (0.34)	0.68 (0.27) [5,8]	0.08 (0.28) [5]

CEC								
Individual Choice	54	48.3 (9.77)	-1.06 (1.04)	-2.26 (1.14)[8]	-2.36 (1.38)	-1.84 (1.59)	-1.07 (1.31)	-1.76 (1.55)
Nutrition	46	48.48 (9.85)	-1.34 (1.16)	-3.33 (1.14)[8]	-1.80 (1.52)	-2.61 (1.53)	0.54 (1.41)	-3.90 (1.46)[8]
Stress Reduction	52	45.44 (11.78)	-4.65 (1.12)[5, 6, 8]	-3.61 (1.18)[8]	-4.36 (1.45)[8]	-4.36 (1.49)[8]	-4.51(1.51)[5,6,8]	-2.96 (1.72)
SCL90/Depression								
Individual Choice	57	0.52 (0.46)	-0.03 (0.06)	-0.23 (0.05)[8]	-0.05 (0.09)	-0.32 (0.08)[8]	0.05 (0.08)	-0.14 (0.08)
Nutrition	51	0.52 (0.43)	0.07 (0.06)	-0.09 (0.05)	0.07 (0.10)	-0.17 (0.08)	0.15 (0.08)[8]	-0.02 (0.07)
Stress Reduction	52	0.66 (0.66)	-0.22 (0.06)[5,6,8]	-0.15 (0.05)[8]	-0.32 (0.09)[5,6,8]	-0.26 (0.07)[8]	-0.07 (0.08)[6]	-0.08 (0.08)
SCL90/Interpersonal/ Sensitivity								
Individual Choice	57	0.36 (0.41)	-0.01 (0.04)	-0.12 (0.05)[8]	-0.01 (0.06)	-0.15 (0.07)[8]	-0.004 (0.06)	-0.11 (0.07)
Nutrition	51	0.40 (0.44)	0.02 (0.05)	0.01 (0.05)[7]	0.04 (0.07)	-0.03 (0.07)	0.03 (0.06)	0.05 (0.06)
Stress Reduction	52	0.43 (0.52)	-0.12 (0.04)[6, 8]	-0.10 (0.05)[8]	-0.18 (0.06)[6,8]	-0.15 (0.07)[8]	-0.08 (0.06)	-0.04 (0.07)
SCL90/Hostility								
Individual Choice	57	0.24 (0.34)	0.05 (0.05)	-0.09 (0.04)[8]	0.04 (0.07)	-0.13 (0.05)[8]	0.04 (0.07)	-0.10 (0.07)
Nutrition	51	0.36 (0.39)	0.03 (0.05)	-0.08 (0.04)	-0.07 (0.08)	-0.17 (0.05)[8]	0.02 (0.07)	-0.07 (0.06)
Stress Reduction	52	0.31 (0.38)	-0.16 (0.05)[5,8]	0.12 (0.04)[8]	-0.20 (0.07)[5,8]	-0.18 (0.05)[8]	-0.10 (0.07)	-0.13 (0.07)
SCL90/GSI General Severity								
Individual Choice	57	0.37 (0.31)	-0.02 (0.03)	-0.11 (0.03)[8]	-0.03 (0.05)	-0.16 (0.05)[8]	0.04 (0.04)	-0.06 (0.04)
Nutrition	51	0.38 (0.32)	0.001 (0.03)	-0.05 (0.03)	-0.001 (0.05)	-0.10 (0.05)[8]	0.02 (0.04)	-0.03 (0.04)
Stress Reduction	52	0.42 (0.35)	-0.12 (0.03)[5,6,8]	-0.07 (0.03)[8]	-0.17 (0.05)[5,6,8]	-0.12 (0.04)[8]	-0.05 (0.04)	-0.02 (0.04)

[1]Adjusted statistically for baseline value, using the General Linear Models procedure in SAS. For the models based on dietary fat we also controlled for social desirability score, which was significantly associated for the 4 month total fat results overall and for women with high expectation.

[2]Values shown are the mean and (standard error).

[3]Baseline mean values did not differ between the groups

[4] This analysis is stratified to include only those subjects the upper half of symptoms based on the BeckD and the upper half of expectancy of a favorable outcome due to randomization condition at study baseline.

[5] Indicates that the stress reduction is different from the individual choice ($p < 0.05$).

[6]Indicates that the stress reduction is different from the nutritional intervention.($p<0.05$).

[7] Indicates that the nutritional intervention is different from the individual choice. ($p < 0.05$).

[8] Indicates that the difference is not equal to zero ($p < 0.05$).

[9] BeckD means reported and statistical tests performed on natural log transformed scores.

WHICH WOMEN WITH BREAST CANCER BENEFIT MOST FROM A MEDITATION-BASED STRESS REDUCTION INTERVENTION: BASELINE DISTRESS AND EXPECTANCY

Lynn Clemow, Ph.D., James Hebert, Sc.D., Ann Massion, M.D., Susan Druker, MA, Yunsheng Ma, M.D., MPH, Jon Kabat-Zinn, Ph.D. University of Massachusetts Medical School

In translating successful psychosocial interventions for women with Breast Cancer to the clinical setting it is important to identify subsets of patients most likely to benefit from specific interventions.

This 3-arm study is a randomized trial of a meditation-based group stress reduction program (SRP) for women with stage I or II Breast Cancer, compared to a a nutrition education program and a standard care control. Overall results (N=158) showed significant beneficial effects of the SRP at immediate post-treatment on Beck Depression scores, SCL-90-R (GSI and several subscales), Active-Behavioral Coping (Dealing with Illness), and Spirituality and other aspects of Quality of Life (QOL). 1-year followup showed sustained benefits of the SRC condition on Spirituality, Active Behavioral Coping, and Emotional QOL (Clemow et al, 1998).

Subset analysis shows that women with high baseline emotional distress (Beck Depression > median) were much more likely to benefit significantly at post-treatment and to have a more enduring effect after 1 year of the SRC vs. comparison conditions on a variety of psychosocial measures including: Higher Active-Behavioral ($p=.01$) and Active Cognitive Coping ($p=.03$) and lower Avoidant Coping ($p=.008$); Less Helpless-Hopelessness ($p=.04$); higher Spirituality ($p=.01$) and Emotional QOL ($p= .005$); higher social support ($p=.003$), and less distress on the GSI and 6 subscales of the SCL-90 ($p=.05$-$.01$). In a different subset analysis, women who reported a high level of expectation of help in the condition to which they were randomized were less likely to show specific advantage of the SRP intervention on psychosocial measures. The findings suggest that baseline emotional distress and beliefs/preferences in the type of program that would feel helpful may significantly modify the effects of behavioral interventions for women with breast cancer.

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CHANGE in DIET and BODY MASS FOLLOWING INTENSIVE INTERVENTION in EARLY-STAGE BREAST CANCER

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ABSTRACT

In a randomized clinical trial (RCT), we studied the effect of an intensive dietary intervention, the Nutrition Education Program (NEP), on changes in diet and body mass in younger (<65 years) women diagnosed with stage I or II breast cancer. In comparison to women randomized to either mindfulness meditation-based stress reduction (SRC) or usual care (UC), there was a large change in fat consumption (% energy as fat) at 4-months (immediately post intervention) (-6.1% vs. no change in either UC or SRC, $p<0.0001$) and much of this change was preserved at 1 year (-4.2% vs. no change, $p<0.0001$). Change in body mass was -1.3 kg at 4 months in the NEP vs. no change in the SRC and UC ($p=0.005$), but did not persist to 1 year. In the subset of women who had higher-than-average expectation of a beneficial effect of the intervention, there were larger changes (-7.7% and -5.3% energy as fat at 4 and 12 months compared to baseline, $p<0.0001$ and $p=0.0002$, respectively) and –1.6 kg of body mass at 4 months ($p=0.002$). This intervention leads to changes in dietary factors, including fat. It also appears to countervail, to some extent, large weight gains generally expected in women with breast cancer. Results in women with high expectations indicate that personal factors may have an important role in modifying the effect of this behavioral intervention and argue for a direct comparison between results obtained in the RCT with those obtained when women are allowed to self-select the NEP.

Key words: breast neoplasms, diet, dietary fats, fiber, body weight, psychology

DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y)

1 JUN 2001

MEMORANDUM FOR Administrator, Defense Technical Information Center (DTIC-OCA), 8725 John J. Kingman Road, Fort Belvoir, VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports. Request the limited distribution statement for reports on the enclosed list be changed to "Approved for public release; distribution unlimited." These reports should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Judy Pawlus at DSN 343-7322 or by e-mail at judy.pawlus@det.amedd.army.mil.

FOR THE COMMANDER:

Encl

PHYLIS M. RINEHART
Deputy Chief of Staff for
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